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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

Transmitted herewith for filing under 37 CFR §1.53(c) is the PROVISIONAL APPLICATION for patent of

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TITLE OF THE INVENTION (280 characters max)

ORGANIC COMPOUNDS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

- ☒ Specification (Including Any Claims and Abstract) - 17 pages
- ☐ Drawings - sheets
- ☒ Other (specify): Application Data Sheet

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Organic Compounds

The present invention relates to drug delivery systems for the prevention and treatment of proliferative diseases, particularly vascular diseases.

Many humans suffer from circulatory diseases caused by a progressive blockage of the blood vessels that perfuse the heart and other major organs. Severe blockage of blood vessels in such humans often leads to ischemic injury, hypertension, stroke or myocardial infarction. Atherosclerotic lesions which limit or obstruct coronary or periphery blood flow are the major cause of ischemic disease related morbidity and mortality including coronary heart disease and stroke. To stop the disease process and prevent the more advanced disease states in which the cardiac muscle or other organs are compromised, medical revascularization procedures such as percutaneous transluminal coronary angioplasty (PCTA), percutaneous transluminal angioplasty (PTA), atherectomy, bypass grafting or other types of vascular grafting procedures are used.

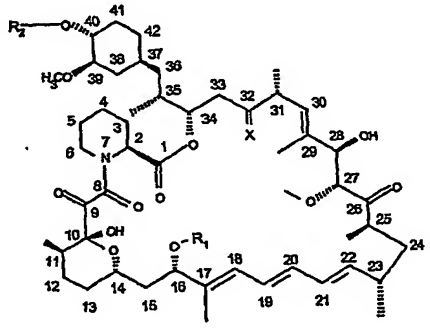
Re-narrowing (restenosis) of an artherosclerotic coronary artery after various revascularization procedures occurs in 10-80% of patients undergoing this treatment, depending on the procedure used and the aterial site. Besides opening an artery obstructed by atherosclerosis, revascularization also injures endothelial cells and smooth muscle cells within the vessel wall, thus initiating a thrombotic and inflammatory response. Cell derived growth factors such as platelet derived growth factor, infiltrating macrophages, leukocytes or the smooth muscle cells themselves provoke proliferative and migratory responses in the smooth muscle cells. Simultaneous with local proliferation and migration, inflammatory cells also invade the site of vascular injury and may migrate to the deeper layers of the vessel wall. Proliferation/migration usually begins within one to two days post-injury and, depending on the revascularization procedure used, continues for days and weeks.

Both cells within the atherosclerotic lesion and those within the media migrate, proliferate and/or secrete significant amounts of extracellular matrix proteins. Proliferation, migration and extracellular matrix synthesis continue until the damaged endothelial layer is repaired at which time proliferation slows within the intima. The newly formed tissue is called neointima, intimal thickening or restenotic lesion and usually results in narrowing of the vessel lumen. Further lumen narrowing may take place due to constructive remodeling, e.g. vascular remodeling, leading to further intimal thickening or hyperplasia.

Accordingly, there is a need for effective treatment and drug delivery systems for preventing and treating intimal thickening or restenosis that occurs after injury, e.g. vascular injury, including e.g. surgical injury, e.g. revascularization-induced injury, e.g. also in heart or other grafts.

It has now been found that rapamycin derivatives having mTOR inhibiting properties, optionally in conjunction with other active compounds, e.g. antiproliferative compounds, have beneficial effects when locally applied to the lesions sites.

Rapamycin is a known macrolide antibiotic produced by Streptomyces hygroscopicus, which inhibits mTOR. By rapamycin derivative having mTOR inhibiting properties is meant a substituted rapamycin, e.g. a 42-substituted-rapamycin or a 16-substituted rapamycin, or a 32-hydrogenated rapamycin, for example a compound of formula I



I

wherein

R_1 is CH_3 or C_{3-6}alkynyl,

R_2 is H, $-CH_2-CH_2-OH$ or 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl, and

X is =O, (H,H) or (H,OH)

provided that R_2 is other than H when X is =O and R_1 is CH_3.

A preferred compound is e.g. 40-0-(2-hydroxyethyl)-rapamycin disclosed in Example 8 in WO 94/09010, or 32-deoxorapamycin as disclosed in Example 1 in WO 96/41807.

According to the invention, the rapamycin derivative may be applied as the sole active ingredient or in conjunction with an immunosuppressive agent, e.g. a calcineurin inhibitor, e.g. a cyclosporin, for example cyclosporin A, or FK506, an EDG-Receptor agonist, e.g. FTY720, an anti-inflammatory agent, e.g. a steroid, e.g. a corticosteroid, e.g. dexamethasone or prednisone, a NSAID, e.g. a cyclooxygenase inhibitor, e.g. a cox-2 inhibitor, e.g. celecoxib, rofecoxib, etoricoxib or valdecoxib, or an ascomycin, e.g. ASM981,

an anti- thrombotic or anti-coagulant agent, e.g. heparin, a IIb/IIIa inhibitor, etc. an antiproliferative agent, e.g.a microtubule stabilizing or destabilizing agent including but not limited to taxanes, e.g. taxol, paclitaxel or docetaxel, vinca alkaloids, e.g. vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides or epothilones or a derivative thereof,e.g. epothilone B or a derivative thereof, a tyrosine kinase inhibitor, e.g. staurosporin and related small molecules, e.g. UCN-01, BAY 43-9006, Bryostatin 1, Perifosine, Limofosine, midostaurin, RO318220, RO320432, GO 6976, Isis 3521, LY333531, LY379196, SU5416, SU6668, AG1296 etc., a compound or antibody which inhibits the PDGF receptor tyrosine kinase or a compound which binds to PDGF or reduces expression of the PDGF receptor e.g. STI571, CT52923, RP-1776, GFB-111, pyrrolo[3,4-c]-beta-carboline-diones, etc., a compound or antibody which inhibits the EGF receptor tyrosine kinase or a compound which binds to EGF or reduces expression of the EGF receptor e.g. the compounds disclosed in WO97/02266, e.g. the compound of example 39, retinoic acid, ZD1839 (Iressa), alpha-, gamma- or delta-tocopherol or alpha-, gamma- or delta-tocotrienol, or compounds affecting GRB2, IMC-C225, a compound or antibody which inhibits the VEGF receptor tyrosine kinase or a VEGF receptor or a compound which binds to VEGF, e.g. proteins, small molecules or monoclonal antibodies generically and specifically disclosed in WO 98/35958, e.g. 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g. the succinate, or in WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819, WO 00/37502, WO 94/10202 and EP 0 769 947, those as described by M. Prewett et al in Cancer Research 59 (1999) 5209-5218, by F. Yuan et al in Proc. Natl. Acad. Sci. USA, vol. 93, pp. 14765-14770, Dec. 1996, by Z. Zhu et al in Cancer Res. 58, 1998, 3209-3214, by J. Mordenti et al in Toxicologic Pathology, Vol. 27, no. 1, pp 14-21, 1999, Angiostatin™, described by M. S. O'Reilly et al, Cell 79, 1994, 315-328, Endostatin™, described by M. S. O'Reilly et al, Cell 88, 1997, 277-285, anthranilic acid amides, ZD4190; ZD6474, SU5416, SU6668 or anti-VEGF antibodies or anti-VEGF receptor antibodies, e.g. RhuMab, a statin, e.g. having HMG-CoA reductase inhibition activity, e.g. fluvastatin, lovastatin, simvastatin, pravastatin, atorvastatin, cerivastatin, pitavastatin, rosuvastatin or nivastatin, a compound, protein, growth factor or compound stimulating growth factor production that will enhance endothelial regrowth of the luminal endothelium, e.g. FGF, IGF, a matrix metalloproteinase inhibitor, e.g. batimistat, marimistat, trocade, CGS 27023, RS 130830 or AG3340, a modulator (i.e. antagonists or agonists) of kinases, e.g. JNK, ERK1/2, MAPK or STAT, or a

compound stimulating the release of (NO) or a NO donor, e.g. diazeniumdiolates, S-nitrosothiols, mesoionic oxatriazoles, a combination of isosorbide.

The present invention also provides the local administration or delivery of rapamycin in conjunction with a calcineurin inhibitor, e.g. as disclosed above, an EDG-Receptor agonist, e.g. as disclosed above, a microtubule stabilizing or destabilizing agent, e.g. as disclosed above, a compound or antibody which inhibits the PDGF receptor tyrosine kinase or a compound which binds to PDGF or reduces expression of the PDGF receptor, e.g. as disclosed above, a compound or antibody which inhibits the EGF receptor tyrosine kinase or a compound which binds to EGF or reduces expression of the EGF receptor, e.g. as disclosed above, a compound or antibody which inhibits the VEGF receptor tyrosine kinase or a VEGF receptor or a compound which binds to VEGF, e.g. as disclosed above, a statin, e.g. as disclosed above, a compound, protein, growth factor or compound stimulating growth factor production that will enhance endothelial regrowth of the luminal endothelium, e.g. as disclosed above, a matrix metalloproteinase inhibitor, e.g. as disclosed above, an inhibitor of a modulator (i.e. antagonists or agonists) of kinases, e.g. as disclosed above, or a compound stimulating the release of (NO) or a NO donor, e.g. as disclosed above.

In accordance with the particular findings of the present invention, there is provided

1. A method for preventing or treating smooth muscle cell proliferation and migration in hollow tubes, or increased cell proliferation or decreased apoptosis or increased matrix deposition in a mammal in need thereof, comprising local administration of a therapeutically effective amount of a rapamycin derivative having mTOR inhibiting properties, optionally in conjunction with one or more other active ingredients, e.g. as disclosed above, or a therapeutically effective amount of rapamycin in conjunction with one or more other active ingredients as disclosed above.

2. A method for the treatment of intimal thickening in vessel walls comprising the controlled delivery from any catheter-based device or intraluminal medical device of a therapeutically effective amount of a rapamycin derivative having mTOR inhibiting properties, optionally in conjunction with one or more other active ingredients, e.g. as disclosed above, or a therapeutically effective amount of rapamycin in conjunction with one or more other active ingredients as disclosed above.

   Preferably the treatment of intimal thickening in vessel walls is stenosis, restenosis, e.g. following revascularization or neovascularization, and/or inflammation and/or thrombosis.

3. A drug delivery device or system comprising a) a medical device adapted for local application or administration in hollow tubes, e.g. a catheter-based delivery device or intraluminal medical device, and b) a therapeutic dosage of a rapamycin derivative having mTOR inhibiting properties or rapamycin, optionally in conjunction with a therapeutic dosage of one or more other active ingredients, e.g. as disclosed above, each being releasably affixed to the catheter-based delivery device or medical device.

   Such a local delivery device or system can be used to reduce stenosis or restenosis as an adjunct to revascularization, bypass or grafting procedures performed in any vascular location including coronary arteries, carotid arteries, renal arteries, peripheral arteries, cerebral arteries or any other arterial or venous location, to reduce anastomic stenosis such as in the case of arterial-venous dialysis access with or without polytetrafluoroethylene grafting and with or without stenting, or in in conjunction with any other heart or transplantation procedures, or congenital vascular interventions.

In a further embodiment, the present invention also provides a drug delivery system or device as disclosed above comprising b) a therapeutic dosage of a compound or antibody which inhibits the PDGF receptor tyrosine kinase or a compound which binds to PDGF or reduces expression of the PDGF receptor e.g. as disclosed above, a compound or antibody which inhibits the EGF receptor tyrosine kinase or a compound which binds to EGF or reduces expression of the EGF receptor e.g. as disclosed above, a compound or antibody which inhibits the VEGF receptor tyrosine kinase or a VEGF receptor or a compound which binds to VEGF, e.g. as disclosed above, each being releasably affixed to the catheter-based delivery device or medical device.

Rapamycin or rapamycin derivative having mTOR inhibiting properties will be referred to heinafter as "drug". The other active ingredients which may be used in conjunction with rapamycin or a rapamycin derivative, e.g. as disclosed above, will be referred to hereinafter collectively as "adjunct". Drug(s) shall mean drug or drug+adjunct.

The local administration preferably takes place at or near the vascular lesions sites.

The administration may be by one or more of the following routes: via catheter or other intravascular delivery system, intranasally, intrabronchially, interperitoneally or eosophagal. Hollow tubes include circulatory system vessels such as blood vessels (arteries or veins), tissue lumen, lymphatic pathways, digestive tract including alimentary canal, respiratory tract, excretory system tubes, reproductive system tubes and ducts, body cavity tubes, etc. Local administration or application of the drug(s) affords concentrated delivery of said

drug(s), achieving tissue levels in target tissues not otherwise obtainable through other administration route.

Means for local drug(s) delivery to hollow tubes can be by physical delivery of the drug(s) either internally or externally to the hollow tube. Local drug(s) delivery includes catheter delivery systems, local injection devices or systems or indwelling devices. Such devices or systems would include, but not be limited to, stents, coated stents, endolumenal sleeves, stent-grafts, liposomes, controlled release matrices, polymeric endoluminal paving, or other endovascular devices, embolic delivery particles, cell targeting such as affinity based delivery, internal patches around the hollow tube, external patches around the hollow tube, hollow tube cuff, external paving, external stent sleeves, and the like. See, Eccleston et al. (1995) Interventional Cardiology Monitor 1:33-40-41 and Slepian, N.J. (1996) Intervente. Cardiol. 1:103-116, or Regar E, Sianos G, Serruys PW. Stent development and local drug delivery. Br Med Bull 2001,59:227-48 which disclosures are herein incorporated by reference.

By "biocompatible" is meant a material which elicits no or minimal negative tissue reaction including e.g. thrombus formation and/or inflammation.

Delivery or application of the drug(s) can occur using stents or sleeves or sheathes. An intraluminal stent composed of or coated with a polymer or other biocompatible materials, e.g. porous ceramic, e.g. nanoporous ceramic, into which the drug(s) has been impregnated or incorporated can be used. Such stents can be biodegradable or can be made of metal or alloy, e.g. NI and Ti, or another stable substance when intented for permanent use. The drug(s) may also be entrapped into the metal of the stent or graft body which has been modified to contain micropores or channels. Also lumenal and/or ablumenal coating or external sleeve made of polymer or other biocompatible materials, e.g. as disclosed above, that contain the drug(s) can also be used for local delivery.

Stents are commonly used as a tubular structure left inside the lumen of a duct to relieve an obstruction. They may be inserted into the duct lumen in a non-expanded form and are then expanded autonomously (self-expanding stents) or with the aid of a second device in situ, e.g. a catheter-mounted angioplasty balloon which is inflated within the stenosed vessel or body passageway in order to shear and disrupt the obstructions associated with the wall components of the vessel and to obtain an enlarged lumen.

For example, the drug(s) may be incorporated into or affixed to the stent in a number of ways and utilizing any biocompatible materials; it may be incorporated into e.g. a polymer or

a polymeric matrix and sprayed onto the outer surface of the stent. A mixture of the drug(s) and the polymeric material may be prepared in a solvent or a mixture of solvents and applied to the surfaces of the stents also by dip-coating, brush coating and/or dip/spin coating, the solvent (s) being allowed to evaporate to leave a film with entrapped drug(s). In the case of stents where the drug(s) is delivered from micropores, struts or channels, a solution of a polymer may additionally be applied as an outlayer to control the drug(s) release; alternatively, the drug may be comprised in the micropores, struts or channels and the adjunct may be incorporated in the outlayer, or vice versa. The drug may also be affixed in an inner layer of the stent and the adjunct in an outer layer, or vice versa. The drug(s) may also be attached by a covalent bond, e.g. esters, amides or anhydrides, to the stent surface, involving chemical derivatization. The drug(s) may also be incorporated into a biocompatible porous ceramic coating, e.g. a nanoporous ceramic coating.

Examples of polymeric materials include biocompatible degradable materials, e.g. lactone-based polyesters or copolyesters, e.g. polylactide; polylactide-glycolide; polycaprolactone-glycolide; polyorthoesters; polyanhydrides; polyaminoacids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g. PEO-PLLA, or mixtures thereof; and biocompatible non-degrading materials, e.g. polydimethylsiloxane; poly(ethylene-vinylacetate); acrylate based polymers or coplymers, e.g. polybutylmethacrylate, poly(hydroxyethyl methylmethacrylate); polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoethylene; cellulose esters.

When a polymeric matrix is used, it may comprise 2 layers, e.g. a base layer in which the drug(s) is/are incorporated, e.g. ethylene-co-vinylacetate and polybutylmethacrylate, and a top coat, e.g. polybutylmethacrylate, which is drug(s)-free and acts as a diffusion-control of the drug(s). Alternatively, the drug may be comprised in the base layer and the adjunct may be incorporated in the outlayer, or vice versa. Total thickness of the polymeric matrix may be from about 1 to 20μ or greater.

According to the method of the invention or in the device or system of the invention, the drug(s) may elute passively, actively or under activation, e.g. light-activation.

The drug(s) elutes from the polymeric material or the stent over time and enters the surrounding tissue, e.g. up to ca. 1 month to 1 year. The local delivery according to the present invention allows for high concentration of the drug(s) at the disease site with low concentration of circulating compound. The amount of drug(s) used for local delivery applications will vary depending on the compounds used, the condition to be treated and the

desired effect. For purposes of the invention, a therapeutically effective amount will be administered. By therapeutically effective amount is intended an amount sufficient to inhibit cellular proliferation and resulting in the prevention and treatment of the disease state. Specifically, for the prevention or treatment of restenosis e.g. after revascularization, or antitumor treatment, local delivery may require less compound than systemic administration.

Preferred combinations are those comprising 40-0-(2-hydroxyethyl)-rapamycin or 32-deoxorapamycin in conjunction or association with a compound having antiproliferative properties, e.g. taxol, paclitaxel, docetaxel, an epothilone, a tyrosine kinase inhibitor, a VEGF receptor tyrosine kinase inhibitor, a VEGF receptor inhibitor, a compound binding to VEGF, a compound having anti-inflammatory properties, e.g. a steroid, a cyclooxygenase inhibitor, ASM981, or with a calcineurin inhibitor, e.g. CysA or FK506. A combination of 40-0-(2-hydroxyethyl)-rapamycin or 32-deoxorapamycin with a compound having anti-inflammatory properties has particularly beneficial effects when used in the treatment or prevention of restenosis in diabetic patients.

Utility of the drug(s) may be demonstrated in animal test methods as well as in clinic, for example in accordance with the methods hereinafter described.

A1. Inhibition of late neointimal lesion formation in the 28 day rat carotid artery balloon injury model

Numerous compounds have been shown to inhibit intimal lesion formation at 2 weeks in the rat ballooned carotid model, while only few compounds prove effective at 4 weeks. Compounds of formula I are tested in the following rat model.

Rats are dosed orally with placebo or a compound of formula I. Daily dosing starts 3 days prior to surgery and continues for 31 days. Rat carotid arteries are balloon injured using a method described by Clowes *et al.* Lab. Invest. 1983;49;208-215. Following sacrifice at 28 days post-balloon injury, carotid arteries are removed and processed for histologic and morphometric evaluation. In this assay the compounds of formula I , e.g. 40-O-(2-hydroxyethyl)-rapamycin, significantly reduce neointimal lesion formation at 28 days following balloon injury when administered at a dose of from 0.5 to 2.0 mg/kg. For example for 40-O-(2-hydroxyethyl)-rapamycin administered at 0.5, 1.0, and 2.0 mg/kg , the percent inhibition is similar at all three doses: inhibition is 31% at the lowest dose (0.5 mg/kg) and 39% at the highest dose (2.0 mg/kg). Compounds of formula I, e.g. 40-O-(2-hydroxyethyl)-rapamycin, have the beneficial effect to inhibit lesions at 4 weeks post-ballooning

A.2 Inhibition of restenosis at 28 days in the rabbit iliac stent model

A combined angioplasty and stenting procedure is performed in New Zealand White rabbit iliac arteries. Iliac artery balloon injury is performed by inflating a 3.0 x 9.0 mm angioplasty balloon in the mid-portion of the artery followed by "pull-back" of the catheter for 1 balloon length. Balloon injury is repeated 2 times, and a 3.0 x 12 mm stent is deployed at 6 atm for 30 seconds in the iliac artery. Balloon injury and stent placement is then performed on the contralateral iliac artery in the same manner. A post-stent deployment angiogram is performed. All animals receive oral aspirin 40 mg/day daily as anti-platelet therapy and are fed standard low-cholesterol rabbit chow. Twenty-eight days after stenting, animals are anesthetized and euthanized and the arterial tree is perfused at 100 mmHg with lactated Ringer's for several minutes, then perfused with 10% formalin at 100 mmHg for 15 minutes. The vascular section between the distal aorta and the proximal femoral arteries is excised and cleaned of periadventitial tissue. The stented section of artery is embedded in plastic and sections are taken from the proximal, middle, and distal portions of each stent. All sections are stained with hematoxylin-eosin and Movat pentachrome stains. Computerized planimetry is performed to determine the area of the internal elastic lamina (IEL), external elastic lamina (EEL) and lumen. The neointima and neointimal thickness is measured both at and between the stent struts. The vessel area is measured as the area within the EEL. Data are expressed as mean ± SEM. Statistical analysis of the histologic data is accomplished using analysis of variance (ANOVA) due to the fact that two stented arteries are measured per animal with a mean generated per animal. A $P < 0.05$ is considered statistically significant.

The compound of formula I, e.g. 40-O-(2-hydroxyethyl)-rapamycin, is administered orally by gavage at a loading dose of 1.5 mg/kg one day prior to stenting, then dosed at 0.75 mg/kg/day from the day of stenting until day 27 post-stenting. In this model, the treatment with the compounds of formula I results in a marked reduction in the extent of restenotic lesion formation: for example, the treatment with 40-O-(2-hydroxyethyl)-rapamycin produces a significant ($P< 0.03$) reduction in neointimal thickness (40% reduction), neointimal area (24% reduction), and percent arterial stenosis (26% reduction) with a significant 32% increase in lumen area. There is extensive neointimal formation in placebo-treated animals at 28 days, with the lesions consisting of abundant smooth muscle cells in proteoglycan/collagen matrix and apparent full endothelial healing. In the majority of arterial segments from the animals treated with 40-O-(2-hydroxyethyl)-rapamycin, the intima is well healed, characterized by a compact neointimal consisting of smooth muscle cells and

endotheluim both over stent struts and between struts. Scanning electron microscopic analysis shows that stented arteries from the animals treated with 40-O-(2-hydroxyethyl)-rapamycin (n = 4 arteries) was 84% endothelialized.

A.3 Inhibition of restenosis at 14 days in the rat carotid stent model

Male Sprague Dawley rats weighing 250 to 500 mg are housed individually and allowed to acclimate prior to surgery. All animals receive standard rat chow and water ad libitum. Group size is 12 animals per group.

The drug(s) administration is perivascular. A segment of ballooned carotid is encircled with a 1 cm length of silastic tubing (0.25 inch inside diameter, .047 inch outside diameter) to which is attached a catheter which feeds into an osmotic pump containing either compound or vehicle. This delivery system provides continuous, local delivery to the adventitia of the wrapped portion of vessel. Local drug(s) administration ranges between 5 µg and 10 mg, locally per day, depending on the solubility characteristics of the individual compounds.

The left common carotid arteries are denuded of endothelium using a 2F Fogarty catheter as previously described (Prescott *Am. J. Pathol.* (1991) 139:1291-1296, Clowes et al., (1983) *Lab Invest.* 49:327-333). Briefly, rats are anesthetized with ketamine (50 mg/ml) and rompun (10mg/ml) administered intraperitoneally at a dose of 1.5 ml/kg. A midline incision is made in the neck to expose the left external and common carotid arteries. The balloon is inserted into the common carotid artery via the left external branch, inflated with saline, and pulled back three times through the lumen with a rotating motion to ensure maximal endothelial denudation. The catheter is then removed, the external carotid artery is ligated and the wound is closed. Each animal is given an injection of the antibiotic Bacillin (200.000 units/kg) and the analgesic Buprenophine (0.06 mg/kg) immediately following surgery.

Animals are killed at 14 days post-balloon injury. One half hour before termination blood is collected, centrifuged, and stored at –20°C for analysis of circulating levels of compound. 5% Evans Blue is then injected intravenously to allow discrimination of re-endothelialized areas at the time of histologic processing. Animals are killed by administration of an overdose of ketamine and rompun, the osmotic pumps are recovered and the volume of remaining content is recorded to ensure that pump failure has not occurred.

Carotid arteries are excised and immersion fixed, then transferred to Ringer's solution. Two samples from control blue region of each left carotid artery are imbedded in paraffin. A minimum of six carotid sections, 20 µM apart are cut per animal and stained with Verhoff

Elastic stain to produce a modified Verhoff stain. Intimal and medial area measurements are performed with a computerized imaging system. The intimal lesion area and the medial area are determined by measurement of the internal elastic lamina, the external elastic lamina and the vessel/lumen interface.

In this assay, 40-O-(2-hydroxyethyl)-rapamycin reduces neointimal lesion formation at 14 days post ballooning when administered locally as disclosed above at a dose of 10 to 200μg/day. Similar good results are obtained when 40-O-(2-hydroxyethyl)-rapamycin is administered in conjunction with dexamethasone (10-250μg/day) or a tyrosine kinase inhibitor.

The following example is illustrative of the invention without limitating it.

A stent is weighed and then mounted for coating. While the stent is rotating, a solution of polylactide glycolide, 0.75 mg/ml of 40-O-(2-hydroxyethyl)-rapamycin, 0.0015 mg/ml 2,6-di-tert.-butyl-4-methylphenol and 1 mg/ml tyrosine kinase inhibitor dissolved in a mixture of methanol and tetrahydrofuran, is sprayed onto it. The coated stent is removed from the spray and allowed to air-dry. After a final weighing the amount of coating on the stent is determined.

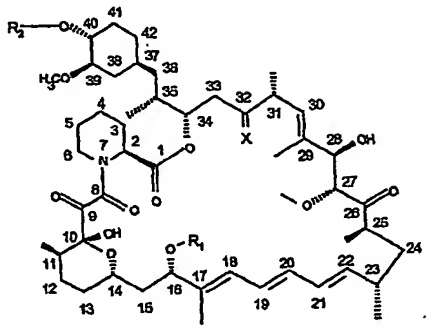
CLAIMS

1. A method for preventing or treating smooth muscle cell proliferation and migration in hollow tubes, or increased cell proliferation or decreased apoptosis or increased matrix deposition in a mammal in need thereof, comprising local administration of a therapeutically effective amount of a rapamycin derivative having mTOR inhibiting properties.

2. A method for the treatment of intimal thickening in vessel walls comprising the controlled delivery from a catheter-based device or an intraluminal medical device of a therapeutically effective amount of a rapamycin derivative having mTOR inhibiting properties.

3. A method according to claim 1 or 2 wherein the rapamycin derivative having mTOR inhibiting properties is administered or delivered in conjunction with one or more other active ingredients selected from a calcineurin inhibitor, an EDG-Receptor agonist, an anti-inflammatory agent, an anti-thrombotic or anti-coagulant agent, an antiproliferative agent, a microtubule stabilizing or destabilizing agent, a tyrosine kinase inhibitor, a compound or antibody which inhibits the PDGF receptor tyrosine kinase or a compound which binds to PDGF or reduces expression of the PDGF receptor, a compound or antibody which inhibits the EGF receptor tyrosine kinase or a compound which binds to EGF or reduces expression of the EGF receptor, a compound or antibody which inhibits the VEGF receptor tyrosine kinase or a VEGF receptor or a compound which binds to VEGF, a statin, a compound, protein, growth factor or compound stimulating growth factor production that will enhance endothelial regrowth of the luminal endothelium, a matrix metalloproteinase inhibitor, a modulator (i.e. antagonists or agonists) of kinases, or a compound stimulating the release of (NO) or a NO donor.

4. A method according to claim 1 wherein the rapamycin derivative having mTOR inhibiting properties is a compound of formula I



I

wherein

R_1 is CH_3 or C_{3-6}alkynyl,

R_2 is H, $-CH_2-CH_2-OH$ or 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl, and

X is =O, (H,H) or (H,OH)

provided that R_2 is other than H when X is =O and R_1 is CH_3.

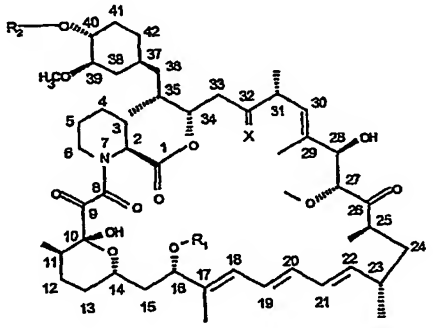
5. A method according to claim 1 wherein the rapamycin derivative having mTOR inhibiting properties is 40-O-(2-hydroxyethyl)-rapamycin.

6. A drug delivery device or system comprising a) a medical device adapted for local application or administration in hollow tubes, e.g. a catheter-based delivery device or an intraluminal medical device, and b) a therapeutic dosage of a rapamycin derivative having mTOR inhibiting properties being releasably affixed to the medical device.

7. A device according to claim 6 comprising b) a therapeutic dosage of a rapamycin derivative having mTOR inhibiting properties in conjunction with a therapeutic dosage of one or more other active ingredients, each being releasably affixed to the medical device and the other active ingredient being selected from a calcineurin inhibitor, an EDG-Receptor agonist, an anti-inflammatory agent, an anti- thrombotic or anti-coagulant agent, an antiproliferative agent, a microtubule stabilizing or destabilizing agent, a tyrosine kinase inhibitor, a compound or antibody which inhibits the PDGF receptor tyrosine kinase or a compound which binds to PDGF or reduces expression of the PDGF receptor, a compound or antibody which inhibits the EGF receptor tyrosine kinase or a compound which binds to EGF or reduces expression of the EGF receptor, a compound or antibody which inhibits the VEGF receptor tyrosine kinase or a VEGF receptor or a compound which binds to VEGF, a statin, a

compound, protein, growth factor or compound stimulating growth factor production that will enhance endothelial regrowth of the luminal endothelium, a matrix metalloproteinase inhibitor, an inhibitor of a modulator (i.e. antagonists or agonists) of kinases, or a compound stimulating the release of (NO) or a NO donor.

8. A device according to claim 6 wherein the rapamycin derivative having mTOR inhibiting properties is a compound of formula I



I

wherein

R_1 is CH_3 or C_{3-6}alkynyl,

R_2 is H, $-CH_2-CH_2-OH$ or 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl, and

X is =O, (H,H) or (H,OH)

provided that R_2 is other than H when X is =O and R_1 is CH_3.

9. A device according to claim 6 wherein the rapamycin derivative having mTOR inhibiting properties is 40-O-(2-hydroxyethyl)-rapamycin.

10. A device according to claim 6 comprising b) a therapeutic dosage of rapamycin in conjunction with a therapeutic dosage of one or more other active ingredients, each being releasably affixed to the medical device and the other active ingredient being selected from a calcineurin inhibitor, an EDG-Receptor agonist, an anti-inflammatory agent, a microtubule stabilizing or destabilizing agent, a compound or antibody which inhibits the PDGF receptor tyrosine kinase or a compound which binds to PDGF or reduces expression of the PDGF receptor, a compound or antibody which inhibits the EGF receptor tyrosine kinase or a compound which binds to EGF or reduces expression of the EGF receptor, a compound or antibody which inhibits the VEGF receptor tyrosine kinase or a VEGF receptor or a compound which binds to VEGF, a statin, a compound, protein, growth factor or compound stimulating growth factor production that will enhance endothelial regrowth of the luminal

endothelium, a matrix metalloproteinase inhibitor, an inhibitor of a modulator (i.e. antagonists or agonists) of kinases, and a compound stimulating the release of (NO) or a NO donor.

11. A method according to claim 1 or 2 wherein the administration or delivery is intravascular, intranasal, intrabronchial, interperitoneal or eosophagal.

12. A method for preventing or treating smooth muscle cell proliferation and migration in hollow tubes, or increased cell proliferation or decreased apoptosis or increased matrix deposition in a mammal in need thereof, comprising local administration of a therapeutically effective amount of rapamycin in conjunction with a therapeutic dosage of one or more other active ingredients, each being releasably affixed to the medical device and the other active ingredient being selected from a calcineurin inhibitor, an EDG-Receptor agonist, an anti-inflammatory agent, a microtubule stabilizing or destabilizing agent, a compound or antibody which inhibits the PDGF receptor tyrosine kinase or a compound which binds to PDGF or reduces expression of the PDGF receptor, a compound or antibody which inhibits the EGF receptor tyrosine kinase or a compound which binds to EGF or reduces expression of the EGF receptor, a compound or antibody which inhibits the VEGF receptor tyrosine kinase or a VEGF receptor or a compound which binds to VEGF, a statin, a compound, protein, growth factor or compound stimulating growth factor production that will enhance endothelial regrowth of the luminal endothelium, a matrix metalloproteinase inhibitor, an inhibitor of a modulator (i.e. antagonists or agonists) of kinases, and a compound stimulating the release of (NO) or a NO donor.

13. A method for the treatment of intimal thickening in vessel walls comprising the controlled delivery from a catheter-based device or an intraluminal medical device of a therapeutically effective amount of rapamycin in conjunction with a therapeutic dosage of one or more other active ingredients, each being releasably affixed to the medical device and the other active ingredient being selected from a calcineurin inhibitor, an EDG-Receptor agonist, an anti-inflammatory agent, a microtubule stabilizing or destabilizing agent, a compound or antibody which inhibits the PDGF receptor tyrosine kinase or a compound which binds to PDGF or reduces expression of the PDGF receptor, a compound or antibody which inhibits the EGF receptor tyrosine kinase or a compound which binds to EGF or reduces expression of the EGF receptor, a compound or antibody which inhibits the VEGF receptor tyrosine kinase or a VEGF receptor or a compound which binds to VEGF, a statin, a compound, protein, growth factor or compound stimulating growth factor production that will enhance endothelial regrowth of the luminal endothelium, a matrix metalloproteinase

inhibitor, an inhibitor of a modulator (i.e. antagonists or agonists) of kinases, and a compound stimulating the release of (NO) or a NO donor.

14. A method according to claim 1 or 2 wherein the administration or delivery is made using a catheter delivery system, a local injection device, an indwelling device, a stent, a coated stent, a sleeve, a stent-graft, polymeric endoluminal paving or a controlled release matrix.

15. A method according to claim 1 wherein the rapamycin derivative having mTOR inhibiting properties is administered from a stent or from a coating applied to a stent.

16. A method according to claim 2 wherein the rapamycin derivative having mTOR inhibiting properties is delivered from a stent or from a coating applied to a stent.

17. A method according to claim 1 or 12 for the treatment of stenosis, restenosis or inflammation.

18. A method according to claim 2 or 13 for the treatment of stenosis, restenosis or inflammation.

19. A device according to claim 6 which is a catheter delivery system, a local injection device, an indwelling device, a stent, a stent-graft or a sleeve.

20. A device according to claim 6 which is a coated stent.

21. A device according to claim 7 or 10 which is a catheter delivery system, a local injection device, an indwelling device, a stent, a stent-graft or a sleeve.

22. A device according to claim 7 or 10 which is a coated stent.

Abstract

The invention relates to the local administration of rapamycin or a derivative thereof, optionally in conjunction with one or more other active ingredients, and a device adapted for such local administration.